

Listing of the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and

b) searching said models using an objective function to select the optimal or near optimal model, wherein said objective function is given by the expression:

Obj + theta penalty · ntheta + random effect penalty · nrand + success · success penalty + covariance · covariance penalty + correlation · correlation penalty.

2. (cancelled)

3. (currently amended) The method of claim [[2]] 1, wherein said search is accomplished by a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm.

4. (currently amended) A method for automated generation of NONMEM/NMTRAN control files from a list of selected features comprising:

a) ~~selecting exactly one feature from each of n sets of mutually exclusive candidate features, wherein n is a positive integer; and, providing a list of selected features, wherein one feature is selected from each set of mutually exclusive features, wherein the selection is done by genetic algorithm, simulated annealing, grid search,~~

integer programming or tabu search; and

b) substituting text associated with each selected feature into a control file template.

5. (currently amended) A method for automated evaluation of the optimality of a model comprising:

combining the log likelihood value with, optionally, a penalty for each parameter estimated, optionally, a penalty for each element of the interindividual variance matrix estimated, optionally, a penalty for each element of the intraindividual variance matrix estimated, optionally, a penalty imposed if the minimization does not conclude successfully, optionally, a penalty if the standard errors of the parameter estimates cannot be obtained, optionally, and a penalty if the correlation matrix of the estimates has any element > 0.95, and optionally a "niche" penalty for being similar to other models in the population (within a "niche radius" of other models); wherein optimality is evaluated using the objective function given by:

Obj + theta penalty · ntheta + random effect penalty · nrand + success · success penalty + covariance · covariance penalty + correlation · correlation penalty.

6. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model and each model is represented by a bit string;

b) assessing the fitness of each candidate model ~~in said population~~;

c) optionally, scaling the fitness of each model to be between and upper limit R and a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

d) providing a number y of models to be in a subsequent generation;

e) selecting with replacement y number of parents of the said subsequent

generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

f) associating said parents into m groups comprising p parents where p is an integer greater than 1;

g) optionally, selecting some fraction of the m groups of parents to undergo at least one cross over;

h) optionally, crossing over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

i) assigning bit strings in current generation that are not selected for cross over to said subsequent generation;

j) optionally, randomly mutate bits of said subsequent generation bit strings wherein said mutation comprises change a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

k) repeating the steps of b through j until further improvement in mean and maximum fitness no longer occurs.

7. (currently amended) The method of claim 6, wherein said ~~initial population is a random population~~ candidate models are randomly generated.

8. (currently amended) The method of claim 6, wherein said fitness is assessed by calculating some statistic of the goodness of fit of the model to the data and adding cost associated with desirable ~~[[atributes]]~~ attributes of the model, including parsimony (fewer parameters).

9. (original) The method of claim 8, wherein the goodness of fit of the model to the data is the log likelihood of the data, given the model.

10. (original) The method of claim 6 wherein the ratio of R to S is between 10:1 and 50:1.

11. (original) The method of claim 6, wherein the number of models in the subsequent generation is equal to the number of models in the current generation.

12. (original) The method of claim 6 wherein $p = 2$.
13. (original) The method of claim 6 wherein said fraction to undergo at least one cross over is selected randomly.
14. (original) The method of claim 6 wherein said fraction to undergo at least one cross over is between 0.4 to 1.0
15. (currently amended) The method of claim 6 wherein said models represent pharmacokinetic models and/or pharmacodynamic models.
16. (original) The method of claim 15 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, $emax$ pharmacodynamic model, linear pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.
17. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models,

comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of the mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and

b) searching the candidate search space using simulated annealing, wherein simulated annealing comprises the steps of:

- i) randomly selecting one model from the candidate search space;
- ii) selecting an initial value for temperature (T) wherein T represents the tolerance of a minimization process for retaining a change in the model that results in a higher energy;
- iii) assessing the energy of the initial model;
- iv) randomly changing the model to generate a subsequent model;
- v) assessing the energy of the subsequent model;
- vi) retaining the subsequent model as the current model if the energy is lower than the current model;
- vii) if the energy of the subsequent model is higher than the energy of the current model the probability of retaining it is equal to:

$$e^{\frac{\Delta E}{KT}}$$

where T is the temperature, ΔE is the change in energy (current model energy – subsequent model energy), and k is Boltzmann's constant, or
Otherwise, rejecting the subsequent model;

- viii) reducing the value of T; and
- ix) repeating the steps of iv through viii until further reduction in energy no longer occurs.

18. (currently amended) The method of claim 17 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of ~~interindividual~~ interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, ~~emax~~ pharmacodynamic model, linear

pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.

19. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of the mutually exclusive features is chosen for each dimension for each candidate model; and

b) searching the candidate search space using full grid search wherein full grid comprises the evaluation of every possible model in the search space.

20. (original) The method of claim 19 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, emax pharmacodynamic model, linear pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship

between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.

21. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and

b) initializing the search with a call to OCLSetup in the OptQuest callable library and initialize a population of models with a call to OCLInitPop;

c) initializing each search dimension with a call to OCLDefineVar in the OptQuest callable library;

d) selecting an initial model from the candidate search space using scatter search/path relinking and tabu search as implemented in the OptQuest Callable library from OptTek systems by calling the function OCLGetSolution;

e) searching the candidate search space using Scatter search/path relinking/Tabu search using the OptQuest Callable library wherein Scatter search/path relinking/Tabu search comprises the steps of:

i) evaluating the fitness of the current model;

ii) adding the value of the fitness of the current model to the OptQuest Callable library database with a call to the function OCLPutSolution;

iii) finding the fitness of the best model thus far evaluated with a call to the function OCLGetBest in the OptQuest Callable Library;

- iv) getting the subsequent model with a call to the function
OCLGetSolution; and
- v) repeating steps i-iv until either the required number of evaluations or
convergence is seen; and
- f) deleting current problem from memory with a call to OCLGoodBye.

22. (original) The method of claim 21 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, emax pharmacodynamic model, linear pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.

23. (currently amended) A computer program product comprising computer usable storage medium having computer readable instructions which when executed on a computer perform a process for selecting ~~that selects~~ a near optimal or optimal mathematical model from a set of candidate models, the computer program product comprising a computer usable storage medium having computer-readable program code embodied in the medium, the computer-readable code comprising:

computer-readable code that is configured to accept a user defined candidate

search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and to search said set of candidate models using an objective function to select the optimal or near optimal model, wherein said objective function is given by the expression:

$$Obj + theta \cdot penalty \cdot ntheta + random \ effect \ penalty \cdot nrand + success \cdot success \ penalty + covariance \cdot covariance \ penalty + correlation \cdot correlation \ penalty.$$

24. (cancelled)

25. (currently amended) The ~~method~~ computer program product of claim 24 wherein said search is conducted using computer-readable code that is configured to search said space for a near optimal or optimal model by a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, tabu search and genetic algorithm.

26. (currently amended) A computer program product comprising a computer usable storage medium having computer-readable instructions which when executed on a computer perform a process for selecting that selects a near optimal or optimal mathematical model from a set of candidate models, the computer program product comprising a computer usable storage medium having computer readable program code embodied in the medium, wherein the computer-readable code is instructions are configured to:

- a) accept user input defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of the mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model and each model is represented by a bit string;
- b) assess the fitness of each model in said population;
- c) optionally, scale the fitness of each model to be between and upper limit R and

a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

d) provide a number y of models to be in a subsequent generation;

e) select with replacement y number of parents of the said subsequent generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

f) associate said parents into m groups comprising p parents where p is an integer greater than 1;

g) optionally, select some fraction of the m groups of parents to undergo at least one cross over;

h) optionally, cross over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

i) assign bit strings in current generation that are not selected for cross over to said subsequent generation;

j) optionally, randomly mutate bits of said subsequent generation bit strings wherein said mutation comprises change a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

k) repeat the steps of b through j until further improvement in mean and maximum fitness no longer occurs.

27. (new) The method of claim 3, wherein said search is accomplished by genetic algorithm.

28. (new) The method of claim 3, wherein said search is accomplished by simulated annealing.